immunization in adults where they are given in a lower dosage than in children, it may be assumed the product is effective in children.

b. *Safety*—(1) *Animal.* This product meets Federal requirements.

(2) *Human.* Most studies in the literature concern adult preparation or combinations including pertussis antigen. In such preparations the rates concerning safety appear adequate.

c. *Benefit/risk ratio.* The benefit-to-risk assessment for this product is satisfactory.

4. *Critique.* A large number of studies (Ref. 3) have been conducted with the Massachusetts' product, as shown in the list of references. Thus, the tetanus and diphtheria toxoids have been shown to be efficacious in primary immunizations in adults using lower doses than those used in children.

Likewise, many studies of reactions to the toxoids have been conducted.

5. *Recommendations.* The Panel recommends that this product be placed in Category I and that the appropriate license(s) be continued because there is substantial evidence of safety and effectiveness for this product.

Diphtheria and Tetanus Toxoids Manufactured by Parke, Davis & Co.

1. *Description.* This is a mixture of diphtheria and tetanus toxoids in 0.85 percent saline solution, containing 2 percent glycerine, purified by filtration, and containing 125 Lf of diphtheria toxoid and 5 Lf of tentanus toxoid per dose. The preservative is thimerosal 1:10,000.

2. *Labeling*—a. *Recommended use/indications.* This product is recommended for prevention of diphtheria and tetanus in children under 6 years (or over 6 if screened with Moloney test). The dose is three injections of 0.5 mL each, intramuscularly or subcutaneously, 3 to 4 weeks apart, and a reinforcing dose about 1 year later. It is recommended for use where a fluid product is preferred. Routine boosters are given preferably at the time of school entrance. For subsequent boosters, the adult type of tetanus and diphtheria toxoids is recommended. Emergency boosters are advised for exposure to diphtheria. For boosters after tetanus-prone injuries, the adult type preparation is recommended.

b. *Contraindications.* Acute febrile illness or treatment with steroids are reasons for postponing inoculation.

3. *Analysis*—a. *Efficacy*—(1) *Animal.* This product meets Federal requirements.

(2) *Human.* No relevant data were presented.

b. *Safety*—(1) *Animal.* This product meets Federal requirements.

(2) *Human.* Ten year old protocols are presented, which are presumably applicable, but this cannot be clearly determined without knowing when the present "purification" procedure was adopted. Temperature rises in protocol 275–1 appear to be abnormally high, i.e., 26 out of 30 subjects show 1° F or higher rises at 24 hours. The manufacturer's covering memorandums of March 11, 1964 (Ref. 4) regarding the investigator's data in protocol 275–1 defines temperature rise so as to allow a final temperature of 0.4° above normal, which gives only 4 rises in 30 subjects. Thus the data are difficult to interpret.

c. *Benefit/risk ratio.* Appears to be similar to that for other combined diphtheria and tetanus toxoids, except that the content of diphtheria toxoid is extraordinarily high. The product is fluid and, therefore, less efficient, and the reaction rate seems high according to the record.

4. *Critique.* This is a fluid combined diphtheria and tetanus toxoid for pediatric use, purified by a somewhat ambiguous method. It contains an excessive quantity of diphtheria toxoid, causing what appears to be more than the expected number of febrile reactions in adult volunteers, and there are not sufficient data to evaluate either its efficacy or safety for primary immunization.

5. *Recommendations.* The Panel recommends that this product be placed in Category I as regards its use for booster immunization and that the appropriate license(s) be continued with the stipulation that the labeling should be revised in accordance with currently accepted guidelines and the recommendations of this Report.

The Panel recommends that this product be placed in Category IIIA as regards its use for primary immunization and that the appropriate license be continued for a period not to exceed 3 years during which time the manufacturer shall be expected to develop data regarding the efficacy of this product when used for primary immunization.

Diphtheria and Tetanus Toxoids Adsorbed Manufactured by Parke, Davis & Co.

1. *Description.* This is an adsorbed combined diphtheria and tetanus toxoid which contains 15 Lf of purified diphtheria toxoid and 5 Lf of purified tetanus toxoid, adsorbed on 2.5 mg of aluminum phosphate per dose. The product contains 0.9 percent sodium chloride and 0.01 percent thimerosal.

2. *Labeling*—a. *Recommended use/indications.* This product is recommended for the primary immunization of children under 6 years of age when a triple vaccine is contraindicated or not recommended. The recommneded schedule is 2 doses of 0.5 mL 4 to 6 weeks apart with a reinforcing dose of 0.5 mL about 1 year later. Recommendations concerning subsequent boosters conform with those of the American Academy of Pediatrics and the Public Health Service Advisory Committee on Immunization Practices. The recommendations regarding "wound boosters" are obsolete, as are the references; the package insert is dated 1970.

b. *Contraindications.* Acute febrile illnesses and courses of immunodepressant—including steroid—therapy are indications for postponing immunization. In addition, the insert recommends a Moloney test and an analogous test with tetanus toxoid before administering this preparation to children over 6 years of age. There is no mention of the use of adult-type tetanus-diphtheria toxoid for boosters.

3. *Analysis*—a. *Efficacy*—(1) *Animal.* This product meets Federal requirements.

(2) *Human.* Brief tabular summaries (Ref. 4) indicate that the product tested in 1961 to 1962 was satisfactory as a booster antigen, with what appears to be a relatively high reaction rate, primarily local (subjects were adults). No primary response data were presented.

b. *Safety*—(1) *Animal.* This product meets Federal requirements.

(2) *Human.* The moderate-to-high reactivity mentioned above was observed in adults; hence, the acceptability of the product for children cannot be assessed.

c. *Benefit/risk ratio.* The benefit-to-risk assessment of this product cannot be satisfactorily assessed, owing to the lack of data in support of the efficacy of this product when used for primary immunization in humans. The benefit-to-risk assessment of this product when used for booster immunization is satisfactory. There was a higher rate of reactions in adults.

4. *Critique.* This product appears to be a typical combined diphtheria and tetanus toxoid product. However, data on the efficacy and tolerance of this product for primary immunization in the age group for which it is indicated are lacking.

5. *Recommendations.* The Panel recommends that this product be placed in Category I as regards its use for booster immunization and that the

appropriate license(s) be continued with the stipulation that the labeling should be revised in accordance with currently accepted guidelines and the recommendations of this Report.

The Panel recommends that this product be placed in Category IIIA as regards its use for primary immunization and that the appropriate license be continued for a period not to exceed 3 years during which time the manufacturer shall be expected to develop data regarding the efficacy of this product when used for primary immunization. Labeling revisions are required.

Diphtheria and Tetanus Toxoids Adsorbed Manufactured by Texas Department of Health Resources

1. *Description.* This product contains 30 Lf of diphtheria toxoid and 20 Lf of tetanus toxoid per mL, adsorbed onto aluminum hydroxide, the content of the latter not to exceed 1.2 mg per mL in the final product. It contains 1:10,000 thimerosal, and the diluent is sodium acetate and buffered saline.

2. *Labeling*—a. *Recommended use/indications.* This preparation is recommended for immunization of children under the age of 6, or in children for whom there is a contraindication for combinations with pertussis vaccine. The dosage for primary immunization is 2 doses of 0.5 mL intramuscular injections at 4 to 6 weeks intervals followed by a third reinforcing dose 12 months later.

The skin should be cleansed with tincture of iodine and alcohol prior to immunizaion.

b. *Contraindications.* These include active respiratory disease or other active infections.

3. *Analysis*—a. *Efficacy*—(1) *Animal.* This product meets Federal requirements.

(2) *Human.* One indirect data are provided (Ref. 5) demonstrating decreased incidence of tetanus and diphtheria in Texas relative to increased distribution of doses of vaccines for these agents.

b. *Safety*—(1) *Animal.* This product meets Federal requirements.

(2) *Human.* The producer states that over the past 10 years many hundred thousand doses of the vaccine were distributed without any serious reactions being reported.

c. *Benefit/risk ratio.* If the product is demonstrated to have satisfactory primary immunogenicity in the age group for which recommended, the benefit-to-risk assessment would be satisfactory for primary immunization, and is satisfactory for booster immunization.

4. *Labeling.* The recommended use is in general agreement with the Advisory Committee on Immunization Practices recommendations. It would be desirable to have the Lf content stated on the label, particularly as it is relatively high.

The recommendations for use of Td adult type for booster purposes is correct but easily misunderstood, since the name of the 2 products are almost identical: "tetanus and diphtheria toxoid, adsorbed (Td)" and "diphtheria and tetanus toxoid, adsorbed." Some of the labeling included in the manufacturer's data submission is illegible.

5. *Critique.* The manufacturer claims the product was patterned after that of the State of Massachusetts and thus controlled studies were not deemed necessary. However, the Lf content is considerably higher (15 Lf for tetanus toxoids, and 10 Lf for diphtheria) than what was used in Massachusetts at the time of this review (according to their submission, 7.5 Lf each of diphtheria and tetanus toxoid for the Massachusetts Public Health Biologic Laboratories' product). Furthermore, the Texas Department of Health Resources uses, aluminum hydroxide, whereas the Massachusetts Public Health Biologic Laboratories uses aluminum phosphate as adjuvant. Labeling regarding the product to be used for boosters is somewhat confusing. There are no human serological studies reported on this product, and the data on lack of reactions appear to be inconclusive.

6. *Recommendations.* The Panel recommends that this product be placed in Category I as regards its use for booster immunization and the appropriate license(s) be continued with the stipulation that the labeling should be revised in accordance with currently accepted guidelines and the recommendations of this Report.

The Panel recommends that this product be placed in Category IIIA as regards its use for primary immunization and that the appropriate license be continued for a period not to exceed 3 years during which time the manufacturer shall be expected to develop data regarding the efficacy of this product when used for primary immunization. Labeling revisions are required.

Diphtheria and Tetanus Toxoids Adsorbed Manufacturer by Wyeth Laboratories, Inc.

1. *Description.* This submission by Wyeth Laboratories includes an excellent summary description of the prepration of the two toxoids. The final product is a combined antigen product including in each 0.5 mL dose 10 Lf of diphtheria toxoid, 5 Lf of tetanus tooid, and 0.34 mg of aluminum as aluminum phosphate. Sodium chloride is used to adjust tonicity of the final product.

2. *Labeling*—a. *Recommended use/indications.* This product is recommended for primary immunization and booster doses of infants and children through 6 years of age. The labeling clearly points out that in most instances a triple antigen (DTP) would be the preferred product. The labeling further differentiates very clearly between this preparation and the adult Td adsorbed preparation.

b. *Contraindications.* Acute active infection is listed as a relative contraindication, except in situations requiring emergency recall or booster doses. An outbreak of poliomyelitis is suggested as a reason to defer elective immunization.

3. *Analysis*—a. *Efficacy*—(1) *Animal.* This product meets Federal requirements.

(2) *Human.* The general body of data supporting the human efficacy of diphtheria and tetanus toxoids is cited (Ref. 6), but no data are provided regarding this particular product as currently produced by Wyeth Laboratories.

b. *Safety*—(1) *Animal.* This product meets Federal requirements.

(2) *Human.* The general body of data regarding the safety of tetanus and diphtheria toxoids is cited, but no data are provided with regard to this specific product as currently produced by Wyeth Laboratories.

c. *Benefit/risk ratio.* The benefit-to-risk assessment of this product when used for primary immunization cannot be precisely determined, owing to the lack of human data supporting its safety and efficacy. The benefit-to-risk assessment of this product when used for booster immunization is satisfactory.

4. *Critique.* The labeling is clearly written, in conformity with current national recommendations, and clearly outlines the preferability of a triple antigen product. References to outbreaks of poliomyelitis as reason for deferral of elective immunization with adjuvant containing vaccines are probably no longer necessary.

The major defect in the submission is the lack of human data supporting the safety and efficacy of this product when used in primary immunization.

5. *Recommendations.* The Panel recommends that this product be placed in Category I as regards the use for booster immunization and that the appropriate license(s) be continued with the stipulation that the labeling should be revised in accordance with currently

accepted guidelines and the recommendations of this Report.

The Panel recommends that this product be placed in Category IIIA as regards its use for primary immunization and that the appropriate license be continued for a period not to exceed 3 years during which time the manufacturer shall develop evidence regarding the efficacy of this product when used for primary immunization.

References

(1) BER Volume 2068.
(2) BER Volume 2028.
(3) BER Volume 2051.
(4) BER Volume 2003.
(5) BER Volume 2098.
(6) BER Volume 2015.

Generic Statement for Tetanus and Diphtheria Toxoids (Td) for Adult Use

See Generic Statement for Monovalent Diphtheria and Tetanus Toxoids.

Description

Tetanus and diphtheria toxoids for adult use (Td) comprises a combination of tetanus and diphtheria toxoids in which the diphtheria component is significantly reduced compared to DT. The diphtheria component is reduced to avoid adverse reactions, such as fever and other systemic manifestations, in individuals who may have had repeated prior exposure to diphtheria antigens and have thus become sensitized to one or more of these antigens. All presently licensed products are adsorbed.

Production

Production of Td follows the same manufacturing procedures as for the individual toxoids and DT, with two major exceptions. The diphtheria toxoid component is reduced to a maximum of 2 flocculation units (Lf) per dose. Also, the purity of the diphtheria toxoid component for this product must be at least 1,500 Lf per mg of nitrogen. The Lf of the diphtheria component of currently licensed products ranges between 1.38 and 2 per dose.

Use and Contraindications

Tetanus and diphtheria toxoids for adult use is designed for two specific purposes. First, it is intended for use as a booster against tetanus and diphtheria in individuals older than 6 years of age, for the reason that it is not recommended to administer pertussis vaccine after this age, and because of possible prior sensitization to the diphtheria toxoid component. In addition to its use as a routine booster, it is recommended for recall booster doses for the prevention of tetanus at the time of injury, at which time it would generally be useful to include enhancement of immunity to diphtheria.

The second purpose for which this combined product is recommended is that of the primary immunization of individuals older than 6 years. The usual recommendations are for the administration of 2 doses of Td at least a month apart, followed by a reinforcing dose approximately 1 year later and booster doses every 10 years thereafter, with appropriate intervening booster doses as recommended by national advisory committees, if injury or diphtheria exposure occurs. Contraindications are the same as for DT.

Safety

In accordance with Federal requirements, both components of Td must be tested for detoxification prior to combination. These requirements are the same as for the individual components and for DT.

Efficacy

The diphtheria component must be tested for potency in animals prior to combination and both toxoids are tested for potency in animals after combination by specified techniques.

The immunogenicity of both components for man is satisfactory for boosters, but the adequacy of the reduced diphtheria component for primary immunization has not been established for all products. Neither the diphtheria nor the tetanus component exerts a significant adjuvant or suppressant effect upon the immunogenicity of the other.

Special Problems

In addition to the problems of individual components (see Generic Statements on Individual Components), a major question is that of the immunogenicity of the smaller amount of diphtheria toxoid as a primary immunizing agent.

Recommendations

Because the same problems associated with the monovalent tetanus and diphtheria toxoids and DT apply to Td, the same recommendations apply with the exception of the issue of purity of the diphtheria toxoid.

In the absence of an animal or other laboratory model that can be interpreted with precision in terms of human immunogenicity, it is imperative that Td be studied in humans to ascertain its effectiveness as a primary immunizing agent against diphtheria.

- *Basis for Classification*

The basis for classification of this combined product is the same as the basis for classification of the individual toxoid components.

References

(1) Public Health Service Advisory Committee on Immunization Practices, "Diphtheria and Tetanus Toxoids and Pertussis Vaccine," *Morbidity and Mortality Weekly Report*, Suppl. 21(25):4–5, 1972.

(2) "Diphtheria—Tetanus—Pertussis," *in* "Center for Disease Control, United States Immunization Survey: 1975," Health, Education, and Welfare Publication No. (Center for Disease Control) 76–8221:25–30, 1977.

(3) Center for Disease Control, "Reported Morbidity and Mortality in the United States 1976," *Morbidity and Mortality Weekly Report*, Suppl., Health, Education, and Welfare Publication No. (Center for Disease Control) 77–8241: 1977.

SPECIFIC PRODUCT REVIEWS

Tetanus and Diphtheria Toxoids Adsorbed (for Adult Use) Manufactured by Eli Lilly Company

1. *Description.* This product contains 7.5 Lf of tetanus toxoid, plus 1.5 Lf diphtheria toxoid per dose in alum at a concentration of 2.55 mg per mL with 0.3 M glycine and thimerosal 1:10,000. The toxin is produced by growth of the organism in casein hydrolysate, and the toxoid is purified by the Pillemer process.

2. *Labeling*—a. *Recommended use/indications.* This product is recommended for primary immunization of adults and children 6 years of age or older against diphtheria and tetanus, two 0.5 mL injections are given 4 to 6 weeks apart and another 0.5 mL dose about 1 year later. Routine boosters are recommended every 10 years.

b. *Contraindications.* Children under 6; acute respiratory disease or other active infections (defer immunization). The labeling includes a cautionary statement regarding use of steroids and after exposure to infections, including tetanus.

3. *Analysis*—a. *Efficacy*—(1) *Animal.* This product meets Federal requirements.

(2). *Human.* No data were submitted to show evidence of immunogenicity for this product.

b. *Safety*—(1) *Animal.* This product meets Federal requirements.

(2) *Human.* A total of nine local and seven systemic reactions have been reported over a 5-year period, during which time many millions of doses were sold. This implies that the product does not have any unusual reactivity.

c. *Benefit/risk ratio.* If the product is demonstrated to have satisfactory primary immunogenicity in the age group for which recommended, the benefit-to-risk assessment would be satisfactory for primary immunization, and is satisfactory for booster immunization.

4. *Critique.* The major problem apparent in review of this product is the lack of evidence for immunogenicity for this specific product when used in primary immunization.

5. *Recommendations.* The Panel recommends that this product be placed in Category I as regards its use for booster immunization and that the appropriate license(s) be continued with the stipulation that the labeling should be revised in accordance with currently accepted guidelines and the recommendations of this Report.

The Panel recommends that this product be placed in Category IIIA as regards its use for primary immunization and that the appropriate license be continued for a period not to exceed 3 years during which time the manufacturer shall be expected to develop data regarding the efficacy of this product when used for primary immunization.

Tetanus and Diphtheria Toxoids Adsorbed (for Adult Use) Manufactured by Lederle Laboratories Division, American Cyanamid Co.

1. *Description.* This is an alcohol-fractionated combined antigen preparation containing 5 Lf tetanus toxoid and 2 Lf diphtheria toxoid per 0.5 mL dose. It contains 2.5 mg per mL aluminum phosphate adjuvant and 0.01 percent thimerosal.

2. *Labeling*—a. *Recommended use/indications.* The product is recommended for active simultaneous primary immunization of adults and children over 6 years of age against tetanus and diphtheria and for subsequent booster immunization.

b. *Contraindications.* Acute respiratory diseases or other active infections. Should not be used under 6 years of age.

3. *Analysis*—a. *Efficacy*—(1) *Animal.* This product meets Federal requirements.

(2) *Human.* No data demonstrating the clinical potency of this specific product were presented. For this manufacturer's product (and similar products from other manufacturers), the suitability of the small 1 to 2 Lf dose of diphtheria toxoid for initiating primary immunization in very young children (beginning at age 7) is undocumented. Claims for efficacy are dependent on experience recorded in the literature for other products.

b. *Safety*—(1) *Animal.* This product meets Federal requirements.

(2) *Human.* No specific data from detailed studies were presented. However, general experience with this type of product is satisfactory, and the manufacturer has recorded a very low level of complaints from consumers.

c. *Benefit/risk ratio.* If the product is demonstrated to have satisfactory primary immunogenicity in the age group for which recommended, the benefit-to-risk assessment would be satisfactory for primary immunization, and is satisfactory for booster immunization.

d. *Labeling.* The statement (under "Precautions") which reads "It should NOT (except in extreme emergency when no monovalent toxoid or antitoxin is available) be used as a therapeutic agent," is ambiguous and should be corrected.

Since Td is the product specifically recommended for "wound booster" doses by the Public Health Service Advisory Committee on Immunization Practices (and other groups), some discussion of its proper use for this purpose alone or in combination with tetanus immune globulin (where appropriate) in tetanus prone wounds is needed.

4. *Critique.* The submission (Ref. 1) is lacking in data to support the use of this product in primary immunization, although it would be unquestionably adequate for booster use. It is especially important to document the suitability of the low dose of diphtheria toxoid for primary immunization of young children (7 and older).

5. *Recommendations.* The Panel recommends that this product be placed in Category I as regards its use for booster immunization and that the appropriate license(s) be continued with the stipulation that the labeling should be revised in accordance with currently accepted guidelines and the recommendations of this Report.

The Panel recommends that this product be placed in Category IIIA as regards its use for primary immunization and that the appropriate license be continued for a period not to exceed 3 years during which time the manufacturer shall be expected to develop data regarding the efficacy of this product when used for primary immunization. Labeling revisions are required.

Tetanus and Diphtheria Toxoids Adsorbed (for Adult Use) Manufactured by Massachusetts Public Health Biologic Laboratories

1. *Description.* This product contains 4 Lf per mL each of diphtheria and tetanus toxoid, 4.0 mg per mL aluminum phosphate, thimerosal 1:30,000 with 0.01 M sodium acetate and 0.1 M sodium chloride as diluent, pH 6.0. Tetanus toxoid is grown on a modified Mueller medium.

2. *Labeling*—a. *Recommended use/indications.* This preparation is recommended for immunization of persons over 6 years of age. A total of 3 intramuscular injections of 0.5 mL each are recommended. Preferably there should be a 12-month interval between the second and third doses.

The product is also used for booster purposes, preferably at 10-year intervals. The recommendations are in general agreement with those of the Public Health Service Advisory Committee on Immunization Practices.

b. *Contraindications.* Acute respiratory diseases, and poliomyelitis epidemics. The concern with poliomyelitis epidemics may be deleted in the label in view of the rarity of such occurrence.

3. *Analysis*—a. *Efficacy*—(1) *Animal.* References to studies in animals of tetanus toxoid with the Massachusetts Public Health Biologic Laboratories' products are given in the manufacturer's data submission to the Panel (Ref. 2). This product meets Federal requirements.

(2) *Human.* The Massachusetts Public Health Biologic Laboratories' products have been tested in the field and data from the 1950's suggest that the recommended doses are highly efficacious as boosters. Also, their efficacy in adults for primary immunization have been established in the paper by Ipsen (Ref. 3).

b. *Safety*— (1) *Animal.* This product meets Federal requirements.

(2) *Human.* References in the submission to studies of reactions to toxoids made by Massachusetts Public Health Biologic Laboratories (Ref. 1) show acceptable low rates of reactions in the recommended doses.

c. *Benefit/risk ratio.* The benefit-to-risk assessment for this product is satisfactory.

d. *Labeling.* The labeling is adequate and up-to-date.

4. *Critique.* Sufficient evidence has been published to demonstrate efficacy and safety in adult use, in the past, both for primary and booster immunizations. Although this product was last tested more than a decade ago and the immune status of the general population may have changed since then with regard to naturally acquired immunity, it may not be possible to obtain more current information on primary immune

responses to Td in adults in the near future.

5. *Recommendations.* The Panel voted after considerable discussion to assign this product to Category I on the basis of the older data with all due recognition of the possible limitations of the applicability of these data to the present day.

Tetanus and Diphtheria Toxoids Adsorbed (for Adult Use) Manufactured by Merck Sharp & Dohme, Division of Merck & Co., Inc.

1. *Description.* This product contains 20 Lf of tetanus toxoid, 4 Lf of diphtheria toxoid, and 2.4 mg of potassium alum per mL in 0.3 M glycine, with thimerosal 1:10,000.

2. *Labeling*—a. *Recommended use/indications.* No packaging insert is provided, no information is given regarding use, no actual labeling is provided (the photo of a label is illegible), and no useful information on the product is submitted.

b. *Contraindications.* No information provided.

3. *Analysis.* No data furnished.

4. *Critique.* No information furnished (Ref. 4) is totally inadequate for an evaluation of this product.

5. *Recommendations.* The Panel recommends that this product be placed in Category IIIC and that the appropriate license be revoked for administrative reasons because this product is not marketed in the form for which licensed and consequently there are insufficient data on labeling, safety, and effectiveness.

Tetanus and Diphtheria Toxoids Adsorbed (for Adult Use) Manufactured by Merrell-National Laboratories, Division of Richardson-Merrell, Inc.

1. *Description.* This product contains up to 4 Lf of diphtheria toxoid and 10 Lf of tetanus toxoid per mL, adsorbed onto aluminum potassium sulfate and preserved with thimerosal in physiologic saline.

2. *Labeling*—a. *Recommended use/indications.* This preparation is recommended for the primary immunization of adults and children of 6 years of age or older. The dose is 0.5 mL given intramuscularly. For primary immunization 2 injections 4 to 6 weeks apart and a third dose 1 year later are recommended. A reinforcing dose every 10 years is recommended. The package insert contains no comment regarding reinforcing doses with injury.

b. *Contraindications.* These include acute illness and an outbreak of poliomyelitis in the community. It is noted that immunosuppressive therapy may interfere with response.

3. *Analysis*—a. *Efficacy*—(1) *Animal.* This product meets Federal requirements.

(2) *Human.* No information directly related to this product is available.

b. *Safety*—(1) *Animal.* This product meets Federal requirements.

(2) *Human.* Over a 5-year period many million doses of this product have been distributed with a total of eight reactions, most of which appear to be minor. The only one of significance includes "paralysis," otherwise undefined.

c. *Benefit/risk ratio.* If the product is demonstrated to have satisfactory primary immunogenicity in the age group for which recommended, the benefit-to-risk assessment would be satisfactory for primary immunization, and is satisfactory for booster immunization.

4. *Critique.* This widely distributed product meets the U.S. standards for animal safety and efficacy and appears to be safe in humans. There is no information regarding its efficacy in humans, other than by analogy with other products. The package insert should include acceptable recommendations about emergency boosters. The inclusion of a community outbreak of poliomyelitis as a contraindication is probably unnecessary at the present time.

5. *Recommendations.* The Panel recommends that this product be placed in Category I as regards its use for booster immunization and that the appropriate license(s) be continued with the stipulation that the labeling should be revised in accordance with currently accepted guidelines and the recommendations of this Report.

The Panel recommends that this product be placed in Category IIIA as regards its use for primary immunization and that the appropriate license be continued for a period not to exceed 3 years during which time the manufacturer shall be expected to develop data regarding the efficacy of this product when used for primary immunization.

Tetanus and Diphtheria Toxoids Adsorbed (for Adult Use) Manufactured by Texas Department of Health Resources.

1. *Description.* This is a combined product containing, per 0.5 mL dose, 10 Lf of tetanus toxoid and 2 Lf of diphtheria toxoid, adsorbed onto aluminum hydroxide, with 0.01 percent thimerosal as the preservative.

2. *Labeling*—a. *Recommended use/indications.* This preparation is recommended for the primary immunization of children over 6 years of age and adults. The recommended course for primary immunization is 2 doses of 0.5 mL intramuscularly at 4- to 6-week intervals with a third dose approximately a year later. Subsequent reinforcing doses are recommended at 10-year intervals. There is no recommendation for a reinforcing dose on occasion of risk from diphtheria or tetanus.

b. *Contraindications.* It is recommended that immunization of individuals with acute respiratory disease or other active infection be deferred. It is stated that the product should not be used for treatment of active tetanus and that the product will not protect against tetanus when given at the time of injury unless the individual has been actively immunized previously. It is also stated that an optimum immune response cannot be expected in individuals receiving immunosuppressive drugs.

3. *Analysis*—a. *Efficacy*—(1) *Animal.* This product meets Federal requirements.

(2) *Human.* No data are available.

b. *Safety*—(1) *Animal.* This product meets Federal requirements.

(2) *Human.* Several million doses were distributed in a 10-year period with no serious reactions reported.

c. *Benefit/risk ratio.* The benefit-to-risk assessment for this product when used for reinforcement of previously established immunity is satisfactory. For primary immunization the risk appears to be low; data relating to the efficacy of this agent for primary immunization are not available and accordingly the benefit-to-risk assessment cannot be established with precision.

4. *Critique.* This combined, adsorbed diphtheria and tetanus toxoid preparation for the immunization of older children and adults would appear to be quite satisfactory for purposes of reinforcement of preexisting immunity. However, there are inadequate data regarding its efficacy for the primary immunization of such individuals.

5. *Recommendations.* The Panel recommends that this product be placed in Category I as regards its use for booster immunization and that the appropriate license(s) be continued with the stipulation that the labeling should be revised in accordance with currently accepted guidelines and the recommendations of this Report.

The Panel recommends that this product be placed in Category IIIA as regards its use for primary immunization and that the appropriate license be continued for a period not to exceed 3 years during which time the manufacturer shall be expected to